

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Changes in QTc Interval After Hydroxychloroquine Therapy in Patients with COVID-19 Infection: a Large, Retrospective, Multi-centre Cohort study
<b>AUTHORS</b>	El Kadri, Moutaz; Al Falasi, Omar; Ahmed, Rizwan; Al Awadhi, Ahlam; Altaha, Zainab; Hillis, Amany; Panikkaveetil, Basheer; Abdalla, Sara; Ansel Benette, Honey; Almubarak, Adhba; Saifuddin, Mohammed; Alattar, Yousef; Oulhaj, Abderrahim; AlKaabi, Salem

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Mensah, Kofi Kwame Nkrumah University of Science and Technology, Department of Pharmacy Practice
<b>REVIEW RETURNED</b>	13-Jun-2021

<b>GENERAL COMMENTS</b>	<p>I commend the authors for a great piece of work because this is the first study to investigate the effect of QT prolongation on the use of HY or HY/AZ in the COVID-19 population. This will serve as a guide for similar works to be done in other regions of the world. Collectively the results will inform health science on the use of HY.</p> <p>The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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<b>REVIEWER</b>	Singh, Maharaj Marquette University, School of Dentistry
<b>REVIEW RETURNED</b>	08-Aug-2021

<b>GENERAL COMMENTS</b>	<p>In introduction section the main justification of the present study was that earlier studies used smaller study sample. The authors should provide some details of the results from similar studies. Statistical analysis provided only descriptive statistics. With such as large study sample it would have better to include a control group with HY and HY/AZ groups.</p> <p>Author did not mention if they used paired test/repeated measure ANOVA for mean QTc prolongation comparison from baseline to the time during therapy.</p> <p>The main objective of the study was hydroxychloroquine induced QTc prolongation and its relation to COVID-19 severity. However, mean QTc prolongation was not analyzed in relation to COVID-19 severity.</p> <p>In the analysis author should use multivariate statistical methods to account of confounding variable including patient demographics and/or clinical parameters.</p>
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	<p>In discussion section some portion of result section was repeated. In this section the results should have been discussed in relation to the result of other similar studies.</p> <p>The manuscript, however presented a good descriptive account of the study population.</p>
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## VERSION 1 – AUTHOR RESPONSE

Comment from reviewer	Reply to Comment
Please note that declarative titles are not part of the journal format. As such, please revise the title of your manuscript to include the research question, study design and setting. This is the preferred format of the journal. See published articles for examples.	Title changed to follow journal house style
Please ensure that you have fully discussed the methodological limitations of the study in the discussion section of the main text.	The limitation section has been incorporated into the discussion section and all relevant weaknesses discussed
In introduction section the main justification of the present study was that earlier studies used smaller study sample. The authors should provide some details of the results from similar studies.	We have modified the introduction to include some results from earlier studies. We tried to keep this relatively short to comply with word count required by the journal. All other relevant studies are referenced within the text and discussed again in the discussion section
Statistical analysis provided only descriptive statistics. With such as large study sample it would have better to include a control group with HY and HY/AZ groups.	While it would be ideal to have a control group, it was not feasible to perform ECGs in patients not receiving HY or AZ as hospitals were overwhelmed with COVID-19 patients and we needed to protect our staff from unnecessary exposure to the virus. To compensate for that we only included in the final analysis patients with ECGs before and after therapy to allow paired measurements. We have added this clarification in the limitation section
Author did not mention if they used paired test/repeated measure ANOVA for mean QTc prolongation comparison from baseline to the time during therapy	We used paired t-test to compare QTc at different time points to baseline QTc (page 7, line 23). We didn't feel that repeated measure ANOVA was a suitable test since not all patients had ECGs everyday (from day 1 to day 5). In fact, the repeated measure ANOVA requires ECG readings to be non-missing at all-time points in order to be used in the analysis (rectangular data). Otherwise, a subject with only one ECG missing will be completely removed. This will create a significant drop in the sample size and eventually will lead to a bias due to a possible non-representativeness of the sample.
The main objective of the study was hydroxychloroquine induced QTc prolongation and its relation to COVID-19 severity. However, mean QTc prolongation was not analyzed	<p>We have changed the title of the study to comply with journal house style and reduced the emphasis on severity in the title (page 1).</p> <p>The extent of QTc prolongation with severity was discussed in the data provided in figure 5 (page10, line 16)</p>

in relation to COVID-19 severity.	
In the analysis author should use multivariate statistical methods to account of confounding variable including patient demographics and/or clinical parameters.	<p>We thank the reviewer for this comment. We have now added a paragraph in the statistical method section regarding the use of multiple linear regression. In these models, the worst QT was considered as the dependent variable and was regressed against each of the main independent variables (mortality and severity of COVID-19), adjusting for available potential confounders such as age, BMI, sex and comorbidity (Page 8, line 1).</p> <p>After adjustment, we found out that the association between QTc and mortality is still significant and the same thing applies to the severity of COVID-19. We reported the results of these multiple linear regression models in the result section (page 10, line 23). We also kept the unadjusted results to be compared to the adjusted ones.</p> <p>The full results of fitting multiple linear regression models are now provided in supplementary material (supplementary Tables 1, 2, 3 and 4) and are attached to reviewers.</p>
In discussion section some portion of result section was repeated. In this section the results should have been discussed in relation to the result of other similar studies.	We have reviewed the discussion and deleted repeated data (unless relevant for the discussion) and restructured the discussion to focus on results from previous studies

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Singh, Maharaj Marquette University, School of Dentistry
<b>REVIEW RETURNED</b>	29-Oct-2021
<b>GENERAL COMMENTS</b>	The authors have addressed my concerns about statistical methodology and description of results.